

UNIVERSITE DE GENEVE
Section de médecine clinique
Institut d'Anesthésiologie

FACULTE DE MEDECINE
Professeur M. GEMPERLE

**URINARY ANTIDIURETIC HORMONE EXCRETION
DURING MECHANICAL VENTILATION
AND WEANING IN MAN**

THESE

présentée à la faculté de médecine de l'Université de Genève
pour obtenir le grade de docteur en médecine —

par

Christian E. VIQUERAT

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La Faculté de médecine, sur le préavis du professeur Marcel Gemperle, autorise l'impression de la présente thèse, sans prétendre par là émettre d'opinion sur les propositions qui y sont énoncées.

Genève, le 31 mai 1979

Le doyen :
André Cruchaud

Thèse No 3753



Je tiens à exprimer toute ma reconnaissance au Professeur M. Gemperle et aux Docteurs P. Suter et M. Hemmer qui ont bien voulu accepter de diriger ce travail.

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A MES PARENTS

Au Docteur Pierre Himmer, chirurgien belge au Zaïre, récemment disparu tragiquement, dont le grand coeur, le dévouement, la gentillesse et principalement la compétence, ont été un exemple pour moi.

ABSTRACT

We measured antidiuretic hormone (ADH) excretion, renal and cardiovascular function in 8 patients with flail chest during four ventilatory conditions : continuous positive pressure ventilation (CPPV), intermittent positive pressure ventilation (IPPV), spontaneous breathing with continuous positive airway pressure (CPAP), spontaneous breathing (SB). Each condition was maintained for 6-8 days.

ADH excretion was greater during CPPV (181 ± 14 ng/24 h., mean $\pm$ SE) than during IPPV (86 ± 10 ng/24 h.), CPAP (83 ± 7 ng/24 h.) and SB (44 ± 6 ng/24 h.). Free water clearance was more negative during mechanical ventilation than during CPAP and SB, resulting in fluid retention during CPPV and IPPV (440 ± 88 ml/day and 547 ± 70 ml/day) and a negative water balance during SB (-154 ± 80 ml/day). Arterial pressure, central venous pressure and cardiac output (measured in 4 patients) did not change significantly between ventilatory conditions.

We conclude that ADH excretion is increased during CPPV and may be a cause of water retention, but its correlation with free water clearance was not linear. ADH release can be secondary to osmotic and intrathoracic volume and/or pressure receptor stimulation.

Abbreviations used in this paper :

ADH	antidiuretic hormone
CPAP	continuous positive airway pressure
CPPV	continuous positive pressure ventilation
IPPV	intermittent positive pressure ventilation
PEEP	positive end-expiratory pressure
SB	spontaneous breathing

INTRODUCTION

Decreased urinary output and fluid retention are frequently observed in patients treated with prolonged mechanical ventilation (1). Intermittent positive pressure ventilation (IPPV) is known to decrease venous return and intrathoracic blood volume (2) and the addition of positive end-expiratory pressure (PEEP) enhances this effect (3, 4). Those hemodynamic alterations presumably activate mechanisms responsible for water retention and changes in urinary output (5, 6). Two mechanisms, suggested by Drury et al. (7) have been studied most : release of antidiuretic hormone (ADH) and changes of renal function. An increase in plasma ADH during continuous positive pressure ventilation (CPPV) has been observed in dogs (8), rats (9), patients in respiratory failure (10), and conscious subjects during IPPV (11). It has been postulated that there are stretch receptors in the left atrium which are sensitive to changes of transmural pressure and vascular volume and which influence urine flow by modifying ADH release (12, 13). Decreased cardiac filling pressures during mechanical ventilation may diminish the neural activity of these receptors and increase the secretion of antidiuretic hormone. The role of the atrial stretch receptors has been challenged, since plasma ADH increased during CPPV in vagotomized dogs also (14).

All of these investigations of the cardiovascular and neurohormonal effects of mechanical ventilation on water and electrolyte handling have been of short duration (hours) and little is known about long term adap-

tation. The purpose of this study was to investigate the effect of mechanical ventilation of several weeks duration and of different ventilatory conditions on ADH excretion, water and electrolyte balance and renal response to ADH.

METHODS

1. Selection of patients

Eight patients, 7 men and 1 woman, ranging in age from 34 to 65 years (mean 56 years) were examined. Mechanical ventilation was required for respiratory failure due to severe flail chest in all cases. The study was started on the third day after admission to the intensive care unit in order to eliminate as much as possible the effects of stress of the first post-traumatic days on ADH secretion. Diuretics and opiates were not given during the study period. Patients presenting with head trauma, central nervous system disease, severe infections, cardiac, liver or renal failure were excluded from the study.

2. Ventilatory conditions

Volume controlled ventilators were used in the assisted mode to deliver a tidal volume of 12 to 15 ml/kg body weight. Studies were performed during four ventilatory conditions, each applied for 6 to 8 consecutive days :

- a) CPPV with a PEEP of 7 cm H₂O
- b) IPPV
- c) spontaneous breathing with a continuous positive airway pressure (CPAP) of 7 cm H₂O
- d) spontaneous breathing (SB).

The sequence of these conditions was a-b-c-d for four patients and b-a-c-d for the other four, established in a random fashion. Measurements were not obtained in 1 patient during CPAP and in 3 patients during SB. Of these, one patient developed a fatal Gram negative septicemia during the CPAP period, 2 other patients had to be transferred to another unit before the end of the study. All patients underwent tracheostomy within 48 hours of admission to the hospital. Radial artery and superior vena cava catheters were placed percutaneously to monitor arterial and central venous pressure. Arterial blood gases and pH were measured several times daily by standard electrode techniques. The inspired oxygen concentration was adjusted to obtain an arterial oxygen tension (PaO_2) between 70-90 mm Hg. Arterial carbon dioxide tension (PaCO_2) was maintained between 35 and 40 mm Hg to avoid the effects of hyper- and hypoventilation on ADH secretion and renal function (15, 16).

3. Fluid and electrolyte balance

All patients received intravenous (glucose, amino-acid and lipid solutions) and intragastric nutrition to ensure an adequate caloric intake. Water balance was calculated from fluid intake minus urinary output and estimated insensible losses. During mechanical ventilation 300 ml was added daily to the water intake as the average gain from the main-line humidifier (1). Mean body surface insensible loss was calculated as 15 ml/hour (17) plus 3 ml/kg body weight/ $^{\circ}\text{C}$ above 37°C (18). A positive or negative water balance was defined as a difference between input and output

after all the above corrections had been applied. Sodium and potassium balance were calculated as intake minus urinary output. For each 24 hour period plasma and urine electrolytes and osmolalities, plasma proteins, blood and urine urea nitrogen, urine and plasma creatinine concentration were measured by standard laboratory technics. Creatinine, free water and osmolal clearances were then calculated.

4. ADH assay

Daily urinary excretion of ADH was measured using a radioimmunoassay for (Arginine⁸)-Vasopressin as reported previously (19). This assay makes use of an anti-serum raised in the author's laboratory whose specificity has been thoroughly tested (20). It is specific for the C-terminal tripeptide chain of arginine-vasopressin and does not bind fragments of this hormone after it has been incubated with kidney homogenate, making thus highly unlikely any interference by urine metabolites. The arginine-vasopressin labelled with 125 Iodine (19) or serving as standard was synthetic arginine-vasopressin obtained from Ferring (Malmö) at a biological concentration of 150 IU/ml. The application of this radioimmunoassay to measurement of urine antidiuretic hormone has been previously validated (21). The mean recovery of unlabelled arginine-vasopressin added to urine and extracted on Amberlite CG 50 (100-200 mesh) was 69.7 ± 1.8 (SE) % with a blank value of 0.29 ± 0.21 pg/ml. The value for normal adults in our laboratory is 70.9 ± 11.1 ng/24 h.

5. Statistical analysis (22)

The results of the first 6 days of each ventilatory condition were analysed for each parameter by the two-way analysis of variance. Linear regression analysis were performed by the method of least squares.

RESULTS

The results are represented as mean values $\pm$ standard error of the mean (SE) for each day during the four ventilatory conditions and are summarized in figures 1 and 2, and tables 1 and 2. The daily fluid volume received by the patients was 32 ± 0.1 ml/kg (mean $\pm$ SE) i.v. or orally. The mean sodium intake was $107 \pm$ mEq per day and of potassium 96 ± 3 mEq per day.

We observed a marked elevation of ADH excretion during CPPV (fig. 1). The urinary output was greater during SB than the other periods. No significant difference in free water clearance was noticed between CPPV and IPPV but an increase was observed when CPAP and SB were instituted. Osmolal clearance did change in opposite direction when compared to free water clearance. The fluid balance was positive during mechanical ventilation and negative during spontaneous breathing (fig. 2). The sodium balance was negative during spontaneous breathing without a noticeable sodium retention during the previous periods. There was no significant change in potassium balance. Creatinine clearance

remained in the normal range throughout the study period. No significant differences were noticed in heart rate, arterial blood pressure, cardiac output and arterial blood gases between the four ventilatory conditions (table 1). Central venous pressure was lower during spontaneous breathing than during CPPV or IPPV. During the transition from IPPV to CPPV (in 4 patients) and from CPPV to IPPV (in the other 4 patients) there was a marked change in the ADH excretion (fig. 3), the ADH being higher during CPPV than during IPPV. The regression line calculated for the correlation between free water clearance and ADH excretion during spontaneous breathing (fig. 4) was similar in our study group and a group of healthy subjects during a salt loading test (21). However the slope of the regression line was significantly different for the data obtained during CPPV : free water clearance = $(-0.065 \times \text{ADH}) - 1.014$ for CPPV, and $(-0.337 \times \text{ADH}) + 0.063$ during SB. Plasma osmolality was higher during CPPV and IPPV than during CPAP (table 2). Plasma sodium concentration was higher during CPPV than during CPAP and SB but no difference between CPPV and IPPV was observed. There was no significant change in plasma proteins and blood urea nitrogen during the study. Urine osmolality was higher during CPPV and IPPV than during the other two periods. A significant decrease was also noticed between CPAP and SB. Urinary sodium excretion was greater during SB than during CPPV, urea nitrogen excretion was higher during CPPV and IPPV than during SB and the total osmolal excretion was higher during CPPV than during SB.

DISCUSSION

We have observed a sustained elevation of urinary ADH excretion during prolonged use of CPPV in adults with chest trauma. Although stress, fear and pain are factors which may increase ADH release in conscious, critically ill patients submitted to mechanical ventilation, these stimuli should not have been different between CPPV and IPPV in our study group. The clinical condition of the patients was similar during the two ventilatory conditions: there was no difference in pulmonary and cardiovascular status.

Thereby we assume that changes in urinary excretion of ADH reflects changes in its secretion from the neurohypophysis, but changes in its metabolic fate cannot be excluded by the present data. We have demonstrated in the rat that ADH injected by micropuncture in the proximal or the distal tubules is recovered intact to the extent of 79 ± 3 or 94 ± 4 % respectively indicating that once filtered ADH is not significantly degraded (28).

The following mechanisms underlying the augmentation of ADH excretion during CPPV must be discussed : first, an osmotic stimulation may have contributed to the increase in ADH release. A positive correlation ($r = 0.57$, $p < 0.001$) existed between the mean values of plasma osmolality and mean urinary ADH levels ; and the regression function describing this relationship : urinary ADH excretion

per 24 hours = 6.7 (plasma osmolality - 272) was similar to that obtained by Fresinaud et al. (23) : 5.9 (plasma osmolality - 275), who used a different urinary assay in healthy men. However the changes observed cannot be explained by this mechanism alone since the major change in ADH excretion occurring between CPPV and IPPV was not accompanied by a significant difference in total plasma osmolality, plasma sodium concentration, water and electrolyte balance or renal function.

Second, ADH secretion and its renal effects can be affected during mechanical ventilation by the application of PEEP : the resulting changes in intrathoracic pressure and blood volume, and the decrease in cardiac filling pressure may increase ADH release through pressor (24) or volume dependant mechanisms (8). There is evidence indicating that a hemodynamic stimulus does not interfere with concurrent osmotic stimuli for ADH release (25). However, the application of PEEP during mechanical ventilation not only effects central blood volume and cardiac output, but may also alter the distribution of cardiac output to and within different organ systems. For instance, there is evidence that PEEP decrease partial blood flow to the central nervous system* and the possibility cannot be excluded that a decreased flow to the hypothalamus itself might be a stimulus for ADH release during CPPV (26). In our patients the

* H. Pontoppidan, personal communication (Stene JK, Snider MT, Boucher R, Wilson RS, Pontoppidan H. : Effects of PEEP on regional blood flow in the awake sheep during spontaneous and mechanical ventilation. Abstracts, Ann. Meet. Am. Soc. Anesthesiologists 1977, p. 711).

renal response to ADH secretion was characterized by a more negative free water clearance during mechanical ventilation (CPPV and IPPV) than during spontaneous breathing (SB and CPAP). This suggests that the water retention observed during mechanical ventilation and the negative water balance during spontaneous breathing could have been at least partly due to modifications in free water clearance secondary to changes of ADH release. In addition, for most values of ADH above 5 ng/hour during CPPV the free water clearance was less negative than would have been expected by linear extrapolation from the relation observed in controls and during spontaneous breathing (21). The disparity between the renal antidiuretic response and the high ADH levels during CPPV have also been observed in the dog (14) and in critically ill patients (10) in short term experiments. The urinary excretions of ADH are considerably above those observed during induced hyperosmolarity (21), and therefore possibly above the range for maximal antidiuretic action. They may reflect plasma concentration at which ADH exerts a vasoconstrictor action, and this could influence its renal effects. In addition, the hemodynamic changes induced by CPPV such as modifications in cardiac output, total renal plasma flow and a redistribution of intrarenal blood flow (10, 27) may also alter the renal response to ADH.

In conclusion, prolonged mechanical ventilation with PEEP is associated with an important and sustained increase of urinary ADH excretion. Fluid retention during prolonged mechanical ventilation and negative water balance after the resumption of spontaneous breathing may be partly due to variations in ADH secretion and consequent changes in free water clearance. Free water clearance is not proportionate to the high ADH levels during CPPV.

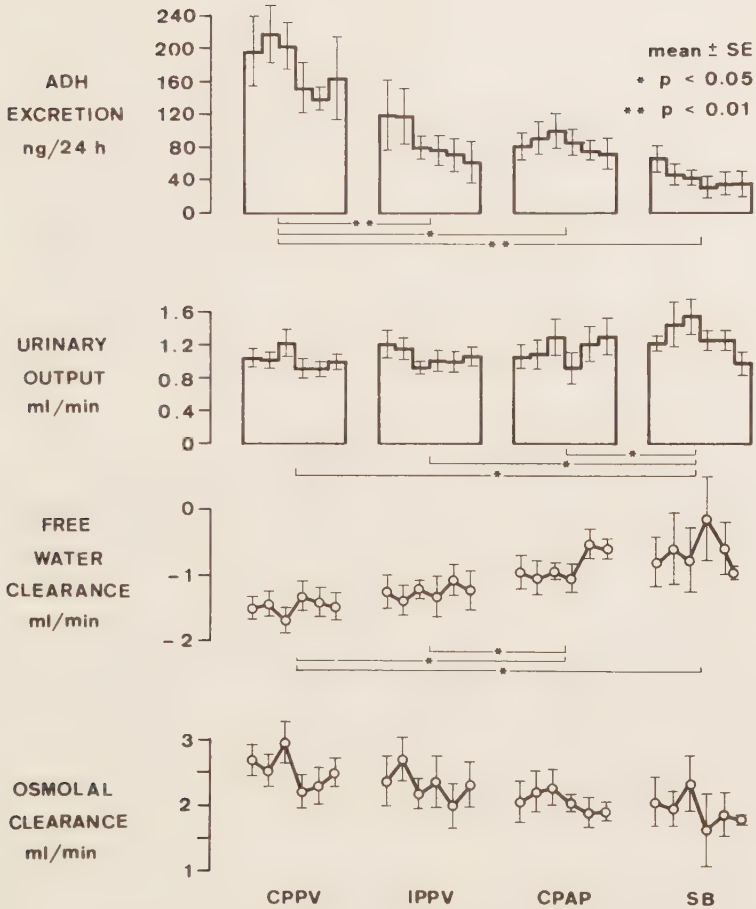


Figure 1 : Effects of the 4 ventilatory conditions on ADH excretion and water handling. The normal value of ADH excretion in our laboratory is 70.9 ± 11.1 ng/24 h (mean $\pm$ SE). Shown are mean values $\pm$ SE. Statistical differences are indicated by the asterisks.

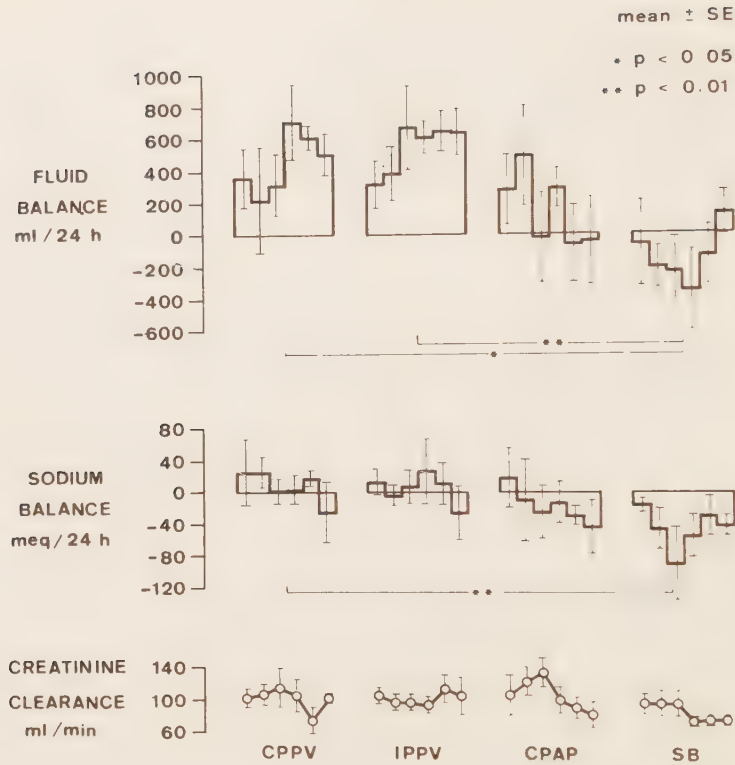


Figure 2 : Effects of the 4 ventilatory conditions on daily water and electrolyte balance.

ADH EXCRETION IN PATIENTS DURING THE TRANSITION

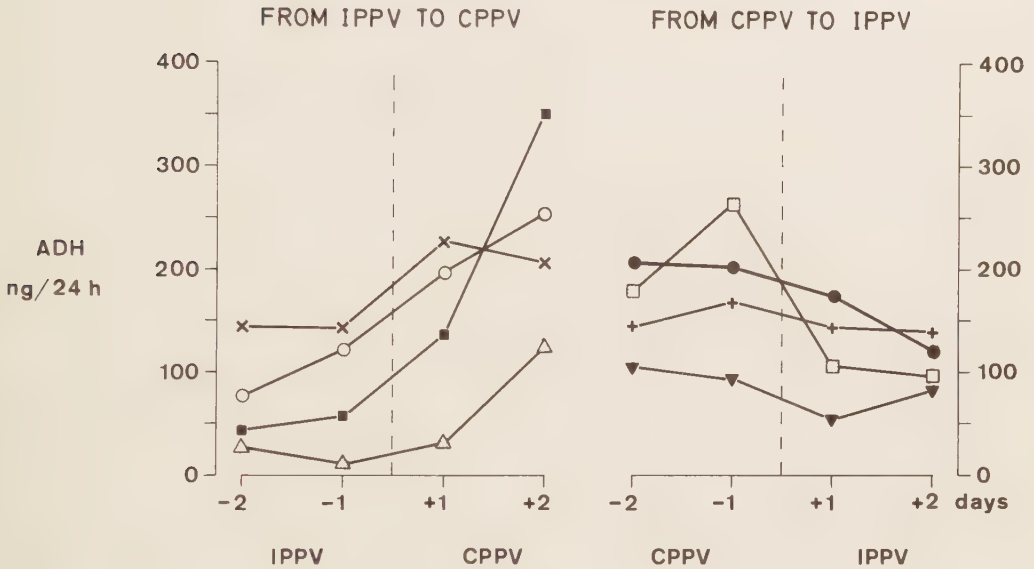


Figure 3 : ADH excretion in the 4 patients during the transition from IPPV to CPPV and from CPPV to IPPV in the other 4 cases. The values of the two days before and after the change of the ventilatory condition are represented.

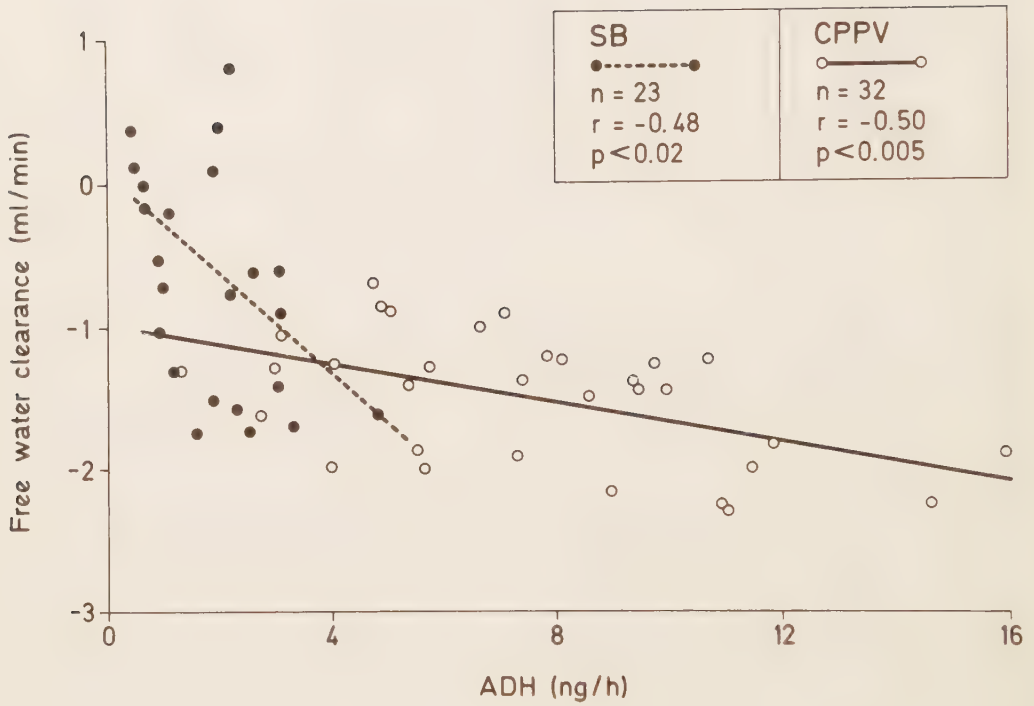


Figure 4 : Relationship between free water clearance and urinary ADH excretion. For CPPV and SB individual points as well as the calculated linear regression lines are indicated.

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